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Acrodynia

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ACRODYNIA

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by

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INTRODUCTION

The paper which I am presenting deals with a disease which is of interest, not only because of recent recognition as a definite clinical entity, but because of its pathological inconsistancies, apparent etiological variances, and contraversal therapeutic responses. These variations, as shall subsequently be seen, have served as a challenge to some of the greatest of medical minds. As a result of their extensive research and objective clinical experimentation, I am happy to be able to compile their data and present it in this paper.

DEFINITION

Acrodynia is a chronic disease of unknown etiology occurring in infants between the ages of six months to four years. It is characterized pathologically by indefinite inconsistent lesions of the central and peripheral nervous systems, and characterized clinically by symptons referable to a disordered function of the vegetative nervous system: namely, tachycardia, sweating, lacrimation, excessive salivation, falling of hair, loss of teeth without involvement of the gums, neurokeratitis, hypotonia, and abnormal contraction of the larger vessels of the hands and feet with capillary dilatation. The onset of the disease is indefinite, running a chronic course after the onset varying from one month to over a year. Intercurrent infections are common but prognosis is relatively good.

HISTORY

Rocez of Bordeaux, in the Archives fur Kinderhulk, drew attention to the fact that Herr Selter reported eight cases of illness in 1903 in which he found no analogy in the literature and which he termed trophodermatoneurosis. The malady occurred in girls one and one-half to three and one-half years of age. He described a typical syndrome of acrodynia as we know it today, and it is without doubt the first report made upon the subject that is complete and authentic enough to make a diagnosis from the report. Evers of India, in 1880, described what is probably this malady as "Ignipedites" or intensely burning feet. No one recognized Selter's or Evers' papers so it remained obscure until 1914, at which time Swift, of Australia, described a symptom complex taken from fourteen of his patients at Aukland before the Children's Section of the Australian Medical Congress. This paper was read by another and its contents were in such detail that little has been added to the symptoms in the present day literature. Swift stated that he had seen the disease entity for many years, but that he had failed to describe it. He termed the disease erythroedema, but stated that the name was unappropriate as a true edema was not present due to no pitting upon pressure.

Clubb a few years later described the disease under the term "Pink Disease" due to the pink hands and feet. A student of William Snowball was present and he and Hobill Cole started to make a collection of cases. In 1920 A. Jeffreys Wood (77) reviewed ninety-one cases of acrodynia from this collection. Snowball's student stated that in 1883 Snowball pointed out to his students a case of "Raw Beef Hands and Feet," but thought it was due to a gastro-enteritis.

In 1920 J. B. Bilderback (2) of Oregon reported a group of cases of unknown etiology and diagnosis. He did not know of the other literature relating to the subject. Patric, one of Bilderback's assistants, sent the paper to J. L. Morse, who suggested pellagra and sent the paper on to William Weston, who was doing quite extensive work on pellagra at that time. Weston (71) recognized that the disease was not pellagra and with his readings related it to the epidemic of Paris in 1827 that had been reported by Chardon. This disease was of unknown etiology, and Chardon termed it acrodynia taken from the two Greek words meaning painful extremities. Weston (71) reported the similarities to this disease in 1920.

In 1917, Byfield wrote a paper but was unable to present it, so in 1919 he again wrote a paper recognizing

a definite clinical syndrome among his patients. In 1920 he gave a very excellent report on these cases under the name of "A Polyneuritic Syndrome Resembling Pellagra - Acrodynia". This was a very good piece of work and even at the present time, with all of the added knowledge, it ranks among the best of the papers on the subject today.

Zahorsky (81) reported two cases in 1920 concerning which there was a question in his mind whether to call them pellagra or acrodynia, having listened to Weston's report in 1920. He again wrote one year later and gave a classical clinical picture of the disease and reported two more cases. In this paper he ridiculed Weston on his comment that the epidemic of Paris was the same type of disease.

In the meantime Karl Petrin, of Sweden, had recognized a disease similar to the "Epideme de Paris" which occurred in Sweden and reported arsenic as the etiological factor. He stated that probably the Paris epidemic of acrodynia, which involved 40,000 people, old and young alike, was also due to arsenic poisoning and had come from wine made from grapes sprayed with arsenic as an insecticide. Weston (71) gives a very accurate discussion on the "Epideme de Paris".

Feer, in 1923, described the disease in Germany

as a vegetative neurosis, the resemblance of acrodynia to a disfunction of the vegetative nervous system. Erickson in the following year again reviewed the subject as Feer's disease and in Germany it is known by this name at the present time.

In England the first to report the condition is Thursfield and Paterson (65) in 1922, and described it under the title of "Dermatopolyneuritis", tending to describe both the cutaneous and polyneuritic symptoms. They give a very good description of the disease entity. Haushalter of France in 1925 described a neurovegetative syndrome in infants. He described the disease and stated that he had seen the syndrome since 1911.

Since 1925 much work has been done and many reports of cases have been made. Amont the best reports in America were those made by Rodda (56), Wycoff, Vipond (67), Zahorsky (83), Orton and Bender (49). The American literature was quite extensive up until the year 1932, from which time it has gradually fallen off, and the main literature has been dealt with by the French and German pediatricians. In the recent literature, Luber and Faber (42) have given an excellent, complete resume on the pa thology found up until the present time.

ETIOLOGY

The etiology of acrodynia is probably as vague and a question as much discussed in the field of pediatrics today as any. Several theories have been formulated as to the etiology of the disease and much has been done in the trend to prove these theories, but so far no proof has been found that leads to the verification of any of them. The original acrodynia that occurred in Paris in 1828 was probably not the acrodynia that is described today and was probably due to arsenic poisoning, as was later shown in similar epidemics in Sweden and England. All we can say is that the etiology is unknown.

The theories as to the etiology that we now have are, namely:

1. Avitaminosis
2. Respiratory Infection
3. Arsenical Intoxication
4. Borax Poisoning
5. Neurosis of Vegetative Nervous System
6. Allergy
7. Grain Fungi
8. Cutaneous Symptom of Encephalitis
9. Combination of Infection and Avitaminosis
10. Abnormal Reaction to Sunshine

Of these theories the infectious theory probably

predominates in the literature of today, followed closely by the theory of avitaminosis with all of the others far in the minority. I shall endeavor to give most of the points that favor the infectious theory and in favor of the avitaminosis, and the discussion made by the literature, both for and against each.

One of the strongest points in favor of the infectious theory is that the disease usually originates in the country, in the better class of people, usually farmers, in which no history can be obtained of any food deficiencies. Practically one-third of the cases occurred in breast fed infants in which the mother had been on a good vitamin diet. Bilderback (2) reported his first cases from a farm community in Oregon where the living conditions and nutritional factor were exceptionally good.

If the disease is an infectious disease, the contagion of the disease is certainly low or the etiological organism is of a low virulence. Only a few cases have been reported in which more than one case appeared in the same household. Wood and Wood (78) reported four families in which the disease was repeated in the inhabitants of the same house, but it occurred fifteen months, three years, four years, and six years apart. This is a longer incubation period than has ever been recorded for any infectious disease. They also report one case in which a baby was

taken to visit a patient who had acrodynia and contracted the malady one month later. I was told the other day that Dr. LeMar, in this state, reports that he has two cases of acrodynia occurring in twins. I do not know the history of these cases but in accordance with the symptoms reported, it is without doubt an accurate diagnosis of acrodynia. The findings of a history of contact, in which the contact was made a reasonable length of time before the first symptoms appeared in the child, is very rare. Talbert (64) reported a case in a three months infant in which the eye infection in the child with acrodynia was similar to that occurring in the mother, but it is not hard to surmise that there can be an overlapping of infections in the disease as in any other condition. In fact, as this disease predisposes to secondary infections, it is without doubt that this is what occurred in this case. Paterson and Greenfield (50) and Rodda (56) classify acrodynia as of infectious origin. Vipond (67), Pehu and Ardison (51), Littlejohn (40), and Kernohan and Kennedy (43) say the naso-pharynx is the portal of entry. The latter two authors claim it is due to the toxic effect of an infection.

Numerous blood cultures have failed to reveal any organisms, with the exception of the occasional presence of a skin staphlococcus. In these cases there was always

a suppurative process occurring in the skin. Vipond (68) did a punch biopsy of an enlarged inguinal gland and found this to contain a gram negative diplococcus which was not typical of any he had ever seen. Of this he made an autogenous vaccine and reported excellent results from its use. He had treated the patients formerly for three months on a high vitamin diet and cod liver oil without much improvement. He went further to say the portal of entry was the nose. May I quote him as saying, "May I say boldly, that acrodynia is a toxemia of the brain and spinal cord due to an unknown organism." Wood (77) found an organism similar to the Shiga dysenteriae in the stools of one patient, and in another was unable to find the organism, but demonstrated a high agglutination property of his serum towards the organism. Penfold, Butler and Wood (53) did a very well executed piece of work with special reference to blood culture using different media. They found small gram positive dyptheroid like organisms. They did not make any definite statement that these were the cause but did state that the organisms were so peculiar as to warrant further examination.

Acrodynia commonly occurs in a child that gives a previous history of infection, and in the review of the American literature, there occurred 80% that gave a

positive infectious history. In most cases it is preceded by a nasal catarrh or an acute upper respiratory infection. Cases have been reported, however, that were preceded by an acute otitis media, which is fairly common, a proctitis, a conjunctivitis of undetermined origin, a regional ileitis, and various infectious mechanisms. Conrad (17) in his report of seven cases stated that four of them followed an upper respiratory infection coincident with an attack of measles, one with a subsequent attack of chicken pox. Tow of the patients had otitis media before the measles infection. Rodda (56) states that in all of his patients there was much evidence of infection and that upon removal of this infection, recovery was prompt and no exacerbations occurred. This will be discussed further under treatment. We are unable to tell if the 20% not reporting a previous infection did not have adequate histories taken, or whether there was no previous evidence of infection.

Some authors state that acrodynia follows a definite influenzal infection. Byfield (11) states that it occurs post-influenzal and that there were more cases after the pandemic of 1918 and after the Paris epidemic of 1827, which he thought at that time was a typical acrodynia as we see it today. Brown, Courtney and MacLachlan (9) were probably the most profound believers of the theory.

some authors have tried to relate the disease to a neurotropic virus infection. Orton and Bender (49) give a summary of those in favor of this theory of etiology. Deuber concluded the cause was a neurotropic virus, as there was a dystonia of the central nervous system on the basis of a constitutional liability and associated with an upper respiratory infection. Trossarelli regarded acrodynia as associated with an encephalitic lesion with predominant mesencephalic localization, to the development of which a certain constitutional liability is a contributory factor. All of this is based upon an infectious basis. Selter maintained the disease was due to a poliomyelitis of the sympathetic nervous system, as there is a definite acute stage followed by a chronic stage. Artom said it was due to a virus similar to poliomyelitis that involved the neuraxis and vegetative nervous system. The American authors have written little on this as an etiological aspect of acrodynia.

Orton and Bender (49) also report Kuhl as relating to the disturbances of the adrenals. He says it is a developmental disorder in the functional relations between the cortex and medulla, giving partly a sympatheticotonic and partly a vagotonic syndrome.

Kernohan and Kennedy (43) by their pa thological report, which was very excellent, state that the disease

is frequently associated with an upper respiratory infection, and the degenerative character in the changes of the nervous system favor the view that the disease is an infection, the toxic products of which secondarily effect the other parts of the body.

Wood and Wood (78) state that the disease comes on when the immunity conferred in utero is lost and this is a contribution toward the infectious theory. They also state that in 24% of their 116 cases there was a temperature of 101° to 102° F., which would favor the infectious theory. One of the outstanding arguments against the infectious theory is its low amount of transmissability. Could this not be explained as Wood and Wood (78) explain it, in that it is due to an infectious virus with a low virulence or a non-pathogenic state? The patients having contact with the disease would build up antibodies counteracting it if the virus was of a low virulence so as to not cause its onset. If the patient had a poor response or the virulence of the organism was increased, the patient would contract the disease. This would explain the infrequency of transmission by direct contact. The papers and reports which might indicate that the condition is due to a vitamin deficiency are few and little has been done to prove the avitaminosis theory. Barbour reported a case in which there was a definite history of vitamin

deficiency, the child eating only milk, cereals, and buttermilk and having never eaten any green vegetables. Vitamin therapy improved this child in three weeks and cured it in six months. Van Westrienen (66) also reported a cure in two months with a high vitamin diet. Szwajkart (63) reported a case of acrodynia superimposed upon a rather severe case of rickets, which would indicate a vitamin deficiency. Among others to report cases with deficiency in the diet are Weston (72), Geissinger (30), Perdman (52) and Clark (14). As I was reviewing the literature, it was very evident that those reporting a vitamin deficiency were by far in the minority in comparison to those reporting an adequate diet. As stated before, the majority of cases were in the rural districts occurring in patients that had either a history of high vitamins, high caloric intake, or had been breast fed.

In a discussion following a paper presented by Dr. Jahr at the Douglas County Medical Society, Dr. Moore agreed with Dr. Jahr in the probability that acrodynia might be due to an infectious element altering the absorption and utilization of vitamins, thus causing a vitamin deficiency and hence acrodynia. If this hypothesis is true, it would be a very reasonable explanation of the frequent histories of infection and to the therapeutic response of the patients to vitamin therapy.

This is one of the most reasonable explanations offered at the present time. Dr. Henske favored only the avitaminosis theory due to the good response to a high vitamin diet and nicotinic acid.

Probably the most important thing done to advance the theory of avitaminosis, was the group of experiments carried out by Findlay and Stern (26) and Paul Gyorgy (34). Findlay and Stern (26) produced a syndrome in rats resembling acrodynia in man, by feeding a complete diet high in known vitamins but the entire source of protein was dried egg white. This produced the typical red feet in the rats, with falling of the hair and typical positions. There was quite some involvement of the mouth and eyes. Boas did this work first and Findlay and Stern repeated it and found the same results. Autopsy results in the rats confirm only slightly those found in acrodynia patients. The fact that young rats suckling mothers with this diet also received the disease, was somewhat characteristic of Pink disease, and also that old rats did not develop the nervous symptoms but did develop the diseased feet. They concluded that both of these were similar in that they occurred in young, had definite nervous and mental symptoms, had a mousy odor and that the pathology affected only the skin and nervous systems. This may develop into a very

interesting piece of work, if followed.

Gyorgy (34) also worked on the avitaminosis theory in combination with temperature. He kept rats on synthetic vitamin B_1 and riboflavine. He found that with a vitamin B_6 deficiency and in cold weather, the rats developed acrodynia-like symptoms, while those on a vitamin B_6 deficiency in normal temperature did not develop the symptoms. Those with the disease he cured quickly with a synthetic preparation of B_6 and concluded that temperature plus B_6 deficiency might be a possible cause of acrodynia.

Now that I have presented both the infectious and avitaminosis theories, I shall summarize the points for and against each.

Infectious Theory

1. Death from secondary respiratory infection.
2. Majority of cases shows previous respiratory infection.
3. Appearance in the United States during the past 19 years.
4. Greater prevalence in some districts.
5. History of good nutrition in majority of cases.
6. Rodda reports removal of tonsils and adenoids gives cures.
7. Onset and pathology similar to other neurotropic

virus diseases.

8. Vipond reports excellent results with autogenous vaccine.

Avitaminosis Theory

1. Findlay and Stern and Gregory produced a similar disease experimentally by deficiencies.
2. No definite microorganisms isolated.
3. Temperature unstable and low.
4. Sedimentation rate normal.
5. Leukocyte count relatively normal.
6. Response by some to vitamins and nicotinic acid.

Arsenic has been suggested as a possible etiological factor, in that it is similar to the Paris epidemic of 1827, which was probably caused by arsenic. Not many, however, adhere to this theory. In the Paris epidemic there was a definitely different clinical entity. Meyer and Weise (45) did some interesting work on this by making complete studies of the excretions, hair and blood for arsenic and lead. They found it to be of high concentration in all. These patients had eaten large amounts of beans previously sprayed with arsenic. They concluded that it might have been the cause of the condition. Calvin and Taylor (12) also found arsenic and lead in the urine in somewhat higher proportion than normal and concluded that this might have been an etiol-

ogical factor. If this is true, why did Barbour's patient clear up so quickly on a high vitamin diet when also receiving Fowler's solution as a therapeutic agent?

Several have adhered to the allergic phenomenon as an etiological agent. Helmick (38) gave a very good report on this with all of the symptoms of acrodynia relating to and connected with the allergic basis. He states that with the absence of the organic findings, the symptoms of eczema, urticaria, rhinitis, asthma and angioneurotic edema could be explained only on an allergic basis.

Geissinger (30) reported cases that he treated with a high vitamin diet, viosterol, and ultra-violet irradiation, with no improvement. He concluded that patients improved without any change of treatment, with apparently nothing influencing the change, and that it is highly suggestive of allergy or neurosis.

Gillespie (31) reported a child with an allergy to milk and eggs, with a continuous eruption over the scalp, face and body, that developed the symptoms of acrodynia, so he thought that allergy might be the cause. The patient, however, had a duodenitis at this time.

The advocates of the allergic basis of etiology are few. It is probably not to be taken too seriously but I do not feel that it can completely be cast aside.

Due to the symptoms of acrodynia relating to the vegetative nervous system, Feer implies that the condition might be due to an imbalance of this system. However, his followers are few. Francioni suggested it to be due to an encephalitic lesion in the diencephalon and mesencephalon, but it is rather hard to conceive of such a complete recovery with a lesion in this area.

Braithwaite (6) considered that the condition might be due to an abnormal reaction to heat, due to the occurrence of the disease in the summer months. He stated that forty-one out of forty-seven cases occurred between March and November and only eight between November and February. He also reported one case that died because the afternoon sun's rays fell upon the patient for a period of one half of an hour. He did quite extensive work with heating blood and tried to prove this, but was unsuccessful.

Sweet disagreed with Braithwaite on the summer incidence and A. J. Wood rejected the work because his patients nursing in the open air and sunshine had a shorter illness. His tanning sun baths were known to be beneficial and in his analysis of one hundred sixteen cases, symptoms did not appear when the sun was at the maximum. The occurrence of the condition in the United States has been limited almost entirely to the northern

portion. Cosmi also reported sixty cases occurring from January to May, which are not relatively sunny months, with a small number of cases occurring in July and August.

To summarize the etiology of acrodynia, there has been very little progressive work accomplished and the etiology is still almost as vague as in 1914, when Swift described the disease. However, I feel that the majority of pediatricians tend to choose either the infectious or avitaminosis theories, and in America the infectious theory still predominates. In Germany they tend to follow the trend taken by Feer, who described the disease as a vegetative neurosis, probably on a functional basis.

INCIDENCE

Acrodynia occurs mainly in infants between the ages of eight and eighteen months. White (75) has reported the only case in adults that has been similar. The disease has been reported in this country as early as three weeks by Wyllie and Stern (79) and as late as seven years by Rodda (56).

Most of the reports would indicate that males predominate slightly. There seems to be no racial predisposition. This was discussed by Zahorsky (84).

Evans (25) in a report of fifty cases, reported that eight percent were in babies of four to six months, seventy-six percent from six to twelve months, twelve percent from twelve to eighteen months and four percent from eighteen months to four years. Of these sixty-six percent were breast fed, ten percent were artificially fed and twenty-four percent had an inadequate dietary history. This was more or less a typical report. The majority of the cases tend to appear in the early winter and spring and in the fall months. Brown, Courtney and MacLachlan (9) reported seven cases, all of which appeared mainly in June and October. The disease occurs most frequently in the rural districts where poverty and neglect were exceptional The seasonal incidence is questionable.

Acrodynia was originally called the "Australian Disease" due to its high incidence in Australia. Since then sporadic cases have been reported in North America, England, France, and Germany. In the United States the cases have appeared mainly in the northern portion, only one case having been presented in the south.

There is no hereditary factor. There is no history of a definite epidemic or endemic factor. Several papers have referred to the disease occurring in various portions of the countries or cities. Zahorsky (67) reports that his cases have occurred in a rather limited district in south St. Louis. The German cases have occurred in a small section in southeastern Germany. The disease varies in England in that most of the cases have occurred in London.

SYMPTOMS

The symptoms of acrodynia are so fixed that even though the cause is unknown and the symptoms resemble many other diseases, the combination of all of the symptoms and findings occur together in such uniformity that the separate disease entity of acrodynia is easily recognized. Swift (3) in his original discussion of the disease gave such an accurate clinical syndrome that almost immediately the men of the Aukland Medical Meeting recognized a newly discovered disease. Sweet (60) stated that he had seen the disease for many years but had been unable to associate the symptoms. If the disease had been present before 1914, it undoubtedly had not been recognized.

The disease has a slow insidious onset. Hutchinson states that it takes three months. The onset, as described, usually varies from weeks to months. Wood and Wood (78), Blackfan and McKhann (4), and Vipond (68) state definitely that the onset of the disease is characterized by an upper respiratory infection and a general malaise. Wood and Wood (78) state that the temperature will be between 100° and 102° F. Cobb (16) explains that sometimes an unexplainable fever occurs a few weeks before the onset. The upper respiratory infection is

recognized in about eighty per cent of the cases. Whether or not the other twenty per cent did not have an upper respiratory infection or whether the histories were incomplete, we do not know. The first symptom syndrome, that is generally recognized by all, is a decided change in personality of the child. A cheerful, happy child will very suddenly change to one that is grouchy and depressed. He will no longer want to play and will sit for hours with a scowl on his face. Nothing seems to attract his attention. In a larger child it may develop unjustified fears and anxieties. The child is fretful and sleep becomes disturbed. He becomes petulant, vicious, and is extremely miserable. The sleep is often disturbed to such an extent that the mother is up night after night, unable to get any rest whatsoever. Butler (10) reports a case that cried constantly and when an attendant came near it would attempt to strike and bite him. The restlessness often continues until the child falls into a drowsiness or coma from sheer fatigue. Youmans (80) described this condition and stated it was due to an excruciating pain in the hands and feet. Crawford (18) states that there are increased periods of irritability and excitability which are followed by apathy and stupor.

During this decided change in the mental state, there

is also a partial or complete anorexia which often makes feeding very difficult. It is necessary at times to resort to feeding by gavage in order to maintain any state of nutrition whatsoever. This anorexia is usually accompanied by profound loss of weight and weakness.

In most papers the onset of the disease is not clearly defined. Most authors tend to base the onset on a basis similar to the psychotic syndrome and change of personality. A few cases have been referred to as having the onset based upon symptoms referable to other than those of the nervous system. McKenzie (47) reported three cases with abdominal pain and marked constipation. Bliss (5) and Clark (14) report cases in which the first symptoms were referable to the rash; Bliss's patient not developing the nervous and mental symptoms until some three months later. Currie (19) reports a typical case that began with a gastro-enteritis with nausea and vomiting and colic-like pain for four weeks before developing the rash. All in all, I do not believe that a definite clinical onset has been established and that a definite diagnosis is impossible, but can only be suspected after the disease is fully established.

Not until the disease is in what Wood and Wood (78) class as the second stage, the stage in which all classical symptoms have developed, does the typical, clear cut

picture exist. This phase of the disease is characterized by the extreme fretfulness and mental changes suggested before, neuro-muscular disturbances, and red rash involving the body and expecially the hands and feet in a typical distribution. It is in this stage that most of the reported cases have been seen for the first time and during this state is the diagnosis quite easily made. This phase of the disease has been quite well described by Byfield (11), Wood (77), Zahorsky (83), Crawford (18), Blackfan and McKhann (4), and Bilderback (3).

Usually after two to three weeks the child breaks out in a profuse perspiration. Following this there develops a generalized or sparce miliary, small, rounded, bright pink or dusky red papules located at the mouths of the sweat glands. The skin between the papules may be somewhat erythematous and cause the eruption to appear similar to a scarlet fever rash. This eruption may, and usually is, more marked on the trunk, abdomen, and buttocks. However, in some instances, it has only been noted on the anterior thorax, outer surfaces of the arms and lateral sides of the buttocks. It may occur on the head and quite frequently on the sides of the neck. These papules may enlarge to two or three millimeters, become flattened and develop a dry, greasy, yellowish-

gray, cap-like scale. The rash may become secondarily infected and form an eczema. Furuncles, abscesses, and paronychias are not uncommon. The child usually, due to the extreme pruritis, causes excoriations and may, by his continual agitation cause bullae or any form of lesions. This eruption commonly shows a tendency towards exacerbations and recurrences. Byfield (11) reported bullae formation on the thorax with a deep phlegmon occurrence in one case. Foerster (27) reported that the papules may even go on into vesicles or pustules.

The hands and feet usually become enlarged and swollen and it is from this that Swift derived the term erythroedema. They become bilaterally involved and first become a bright red, later assuming a dusky purplish red. Blackfan and McKhann (4) describe the condition as a red, dull, frost-bitten appearance with intense itching and burning. The distribution is usually very typical, the erythema covering first the palmer and plantar surfaces of the fingers and toes and extending over the dorsal surfaces. Paterson and Greenfield (50) describe it as beginning as a fine desquamation of the palms and soles and gradually extending to the tips of the fingers and toes. The rash gradually fades proximally before reaching the wrists or ankles or, at the most, it is very faint. Pressure reveals a very slow return of blood to

the capillaries. The sweating is usually profuse on the hands and feet, and when one takes hold of the reddened extremities it surprises him to find that they have a cold, sodden, cadaverish feel. The fingers become swollen, oblong, and sausage shaped. The epidermis becomes thickened and sodden and the extreme rubbing the little patient does often causes it to become macerated. A process of exfoliation is continually going on, mainly on the palmer and planter surfaces of the fingers and toes. The cracks and the erosions give the "raw-beef" appearance described by Snowball. Many authors, including Cobb (16), describe the trophic changes of the fingers and toes, and Weber (70) reported a very extreme case in which the fingers were cyanotic and later developing ulcerations and gangrene with the subsequent loss of three fingers. The edema that is present is not of the pitting type and hence it was questioned for a long time whether or not it was a true edema. The loss of finger and toe nails has been recorded in various instances but it does not occur very often. The fingers and toes are so painful that they continually rub them, either together or against the bedding. They also may rub the nose, eyes, genetalia, or anus. It seems to relieve the condition a great deal if they can put the hands and feet in cold water or out of the window into the cold air. The

children show almost a maniacal desire to thrust the fingers and toes into the mouth, sometimes actually chewing them. I quote Weston (71). "Such a picture of abject misery once seen will never be forgotten." The neuro-muscular symptoms are greatly pronounced at this stage. As I have previously covered the mental symptoms, I shall not endeavor to cover them at this time, but they are often greatly intensified. There also seems to be quite a discrepancy in attempting to classify the symptoms under a disturbance of the vegetative nervous system and I will not, in my discussion, attempt to include the various classifications but shall only touch on them later in the paper. Asthenia, which is quite pronounced, is one of the most prominent neuro-muscular symptoms. One of the first things noticed is that the child develops an extreme weakness, which is gradually progressive. Some of the patients gradually develop a complete paralysis of the lower extremities, which gradually clears up in about four months after recovery. Schwartz (57) reports one of these cases with flaccid paralysis of the lower extremities. However, Wood (77) states that a paralysis never goes to such an extent that the patients can't walk. Paterson and Greenfield (50) report a case with such weakness of the muscles of mastication that the patient was unable to hold up the lower jaw. Many

think that the characteristic attitudes assumed by these children are due to the neurosthenia. The child usually sits up and lets the body bend forward until the head is between the legs and in close proximity to the feet. Another attitude assumed is that of resting on the knees with the knees flexed upon the abdomen and the face buried in a pillow. Many say the conditions are assumed due to the extreme photophobia which accompanies the disease and many assume the later attitude to be due to extreme abdominal pain. The cause of the position assumed by the patients is a variance of opinions and cannot be stated for sure. The reflexes are increased indicating a hyperirritability of nerves, but these later get sluggish and sometimes are completely absent in the more pronounced stages of the disease. Paterson and Greenfield (50) states that the knee jerks were absent in one hundred per cent of their cases. In all of the reported cases the soft, flabby, hypotonia of the muscles was one of the constant findings and can be well thought of in making a diagnosis of acrodynia. The paresthesia present is one of the most agitating subjective symptoms. These abnormal sensations along with the extreme pain present causes the marked insomnia and hyperirritability. The patients are constantly tossing about and rubbing the hands and feet together and have the faces of an old man

in melancholia. The patient is often so mentally disturbed as to have a trichotillomania and may at times have a partial alopecia or a complete alopecia. Alopecia also occurs presumably on the basis of a dysfunction of the sympathetic system. There is also a complete anesthesia on some patients, especially on the extremities. Vipond (68), in making a punch biopsy of an inguinal lymph gland without anesthesia, stated that the child felt no pain. Butler (10) states that a biopsy taken from the foot without anesthesia gave no pain. The paresthesias occur over the entire body including the hands, feet, ears, nose, mouth, genitals, anus, etc., and may account for the rubbing of the head in the pillows to such an extent as to cause hyperemia and edema of the nose and cheeks. However, some authors state that this condition of the face is the same as that on the hands and feet. There is always an increased sweating and it may become so profuse as to require a change of the bed clothes every few hours. Sweating usually precedes and may be the cause of the rash that is present.

There is an extreme photophobia which accompanies the condition and has been noticed by many observers. The child usually turns away from the light and assumes the attitude previously described. Byfield (11) states

that when the mother carries them, they will bury their heads in their mother's breasts. This photophobia usually appears early and lasts for several months with periods of regression. The eyes appear lusterless and dull, and a watery discharge develops that tends to produce redness and congestion of the margins of the eyelids and mild conjunctivitis, keratitis and optic atrophy have been reported.

In the ear the most common symptom is otitis media, which is so often reported. It may occur preceding the classical symptoms or after they have been established. However, it is probably secondary to the nasopharyngitis which accompanies almost every case. In some cases that have paresthesias of the pinna of the ear, they tend to rub and pull the ears with their macerated, edematous hands and thus produce a hyperemia with maceration of the pinna.

The symptoms referable to the respiratory tract may be many and varied. It probably is a secondary infection but may be the primary invasion. Almost invariably there is a serous nasal discharge or rhinorrhea. In one case reported by Weber (70) there was almost an entire atrophy of the septum and turbinates without any history of syphilis and with no sequestra formation. Obstruction of the breathing from a hypertrophic nasal membrane

is very frequent. A pharyngitis and bronchitis are frequently present and the onset of the disease, being so commonly associated with these symptoms, leads many to believe a neurotropic virus to be the cause. This has been discussed previously. Cough is usually absent due to a hyposensitive mucous membrane. One of the most common complications of the disease is broncho-pneumonia and this is usually the cause of many of the fatalities associated with the malady. The cutaneous nasal symptoms are previously described.

The symptoms relating to the gastro-intestinal tract are probably the most inconsistent and varied of any of the systems. Anorexia is always present and may be the cause of the myasthenia that accompanies it. It is one of the first symptoms to appear and one of the first symptoms to leave when progress is noted to be improved. Sialorrhea is present and may cause an incessant drooling of the mouth. The children are sometimes constipated and sometimes have a marked diarrhea. It has been the experience of the observers that constipation was predominant and when diarrhea was present, there was usually an infection lower in the gastro-intestinal tract. The cause of the constipation has been said to be due to a diminished autonomic reflex or to dehydration that is invariably present. The

tongue is often a deep beefy red and may be slightly swollen and fissured. Some children actually chew the tongue. The gums may appear quite normal but may appear swollen and congested. Wyllie and Stern (79) report a case that at the end of the third month was showing improvement but as the mother pulled down the lower lip to expose the teeth, the gums fell away from the teeth exposing their roots. The gums had previously appeared normal. Also recorded several times is the process of loosening and falling out of the teeth without involvement of the gums or any demonstrable gum pathology. This may take place in the permanent teeth as well as in the deciduous teeth. The buccal mucosa is often red and swollen, and some children develop the vicious habit of chewing the inner surface of the cheek producing inflamed, necrotic and ulcerating lesions. Necrotic stomatitis has been reported by many observers and has been found in almost all of the cases reported. Abdominal pain has been said to be excruciating in some instances, but I would say it is in the minority. Vomiting is not common. Physical examination of the abdomen is invariably negative with flaccidity and retraction of the abdominal wall. Proctitis occurs in some of the cases. The anus may show extensive ulceration from traumatic rubbing due to paresthesias. Prolapse of the

rectum, due either to straining at stool or myasthenia, has been noticed in several instances. Stool examinations were invariably negative.

The consistent findings of the cardio-vascular system are the elevated blood pressure and tachycardia. The blood pressure ranges from 100 to 120 mm. of mercury and the pulse ranges from 120 to 160 beats per minute and is always out of proportion to the temperature which lingers around 100 degrees and is rarely above 102 degrees Fahrenheit unless a superimposed infection is present. The heart musculature and sounds are normal in a majority of cases.

Dysuria is usually present. It is probably due to the concentrated urine passed. A cystitis and pyelitis are common complications, but are easily cured. The dysuria is often acutely painful and frequent. It has been explained on the basis of a neurogenic functional disturbance.

Byfield (11), Crawford (18), Braithwaite (6) and Blackfan and McKhann (4) all reported a generalized lymphadenopathy.

Some have reported that the cases always have a characteristic mouse-like odor. However, this has been denied by others.

The laboratory work has revealed very little to

help with the diagnosis, etiology or prognosis of the disease. Urine analysis is usually negative. The blood count is usually increased, ranging from 5,000,000 to 6,000,000 red cells per cubic millimeter and 12,000 to 40,000 white blood cells per cubic millimeter, depending upon the intercurrent infection that happens to be present. The differential count is usually normal, there sometimes being a shift to the left. Byfield (11) reports his cases to have an average eosinophilia of five per cent. The increased red count is probably due to the dehydration present. Blood cultures are invariably negative. Wassermann, Mantoux and Von Pirquet tests were also negative. Feces examinations have never revealed any ova but history of round worm infections was present in two case reports. Braithwaite (6) reports that the blood calcium is slightly but definitely raised while Perlman (52) reports a case of quite low blood calcium. Brown, Courtney and MacJachlan (9) report a normal blood calcium. Blackfan and McKhann report a frequently high blood sugar with a low glucose tolerance. They also seem to have done tests which others have not, such as to find achlorhydria in two cases out of seventeen and a normal response to histamine in the rest. The basal metabolic rate in one was plus sixty but the others were normal in the ones on

which they were able to do the test. They reported albuminuria in one case out of ten and glycosuria in fourteen cases of the seventeen. Spinal fluid findings have varied but the fluid has always been clear and of normal pressure. The cell count is normal. Blackfan and McKhann (4) reported that protein as high as 250 milligrams per cent was found and the globulin was increased in one of the seventeen cases. The sugar was normal in nine cases and abnormal in eight cases. They stated that this might indicate a degenerative or a mild inflammatory process.

Brown, Courtney and MacJachlan (9) made studies of the urine and the feces with special reference to the nitrogen balance and found it to be negative in two cases. They attributed this to a chronic upper respiratory infection.

Bacteriological cultures have been run many times, but as the majority of them have been discussed I will not endeavor to do so here.

Various classifications of symptoms have been discussed, but as in nephritis, none can be selected. Wood and Wood (78) classify the symptoms in three stages, there being a period of onset, a period during which all of the classical symptoms are present and a period of convalescence or gradual recovery. Rodda (56) puts the

symptoms under three general divisions. He states that there are the general symptoms of anorexia, loss of weight and weakness, accompanied by the nervous symptoms of hyperirritability, sleeplessness, paresthesias, anesthesias, loss of reflexes, paresis and photophobia and the dermatographic symptoms of hyperhidrosis, miliaria, desquamation, erythema, swelling, cyanosis, coldness of hands and feet, alopecia, ulceration and loss of teeth. Blackfan and McKhann made an excellent resume of all of the symptoms and pointed out the role played by various parts of the system and how the symptoms of acrodynia can be associated with the dysfunction of these parts. It was so well done that I am taking the liberty to include it here.

I. Symptoms of Cerebral or Spinal Involvement
   a. Apathy
   b. Muscular weakness and paralysis
   c. Deep muscle pains

II. Symptoms Probably Cerebral or Spinal but Probably Due to Autonomic Nervous System
   a. Hypermobility and hypotonia
   b. Hyperesthesia
   c. Coma and convulsions

III. Autonomic Involvement

a. Sympathetic disturbances (overactivity)

1. Vaso-motor disturbances (hands, feet, less marked on trunk)
2. Dilatation of pupil and photophobia
3. Tachycardia
4. Sweating
5. Falling of hair
6. Hypertension
7. Elevated blood pressure

b. Autonomic involvement probably due to parasympathetic and not definitely assignable to sympathetic

1. Salivation
2. Rhinorrhea
3. Vomiting
4. Abdominal pain
5. Hypomotility alternating with hypermotility of gastro-intestinal tract.
6. Constipation
7. Difficult Micturition

IV. Secondary Involvement

a. Maceration of skin due to profuse sweating

b. Secondary infection

c. Dehydration due to excessive water loss

1. Elevated blood pressure

2. Elevated serum protein

3. Concentrated urine

4. Constipation

d. Loss of weight with a negative nitrogen balance

I do not say that this outline would be acceptable by all of the authorities, and probably would, on the other hand, receive much criticism, but it does endeavor to show that the symptoms of the disease are related to a definite pathological physiology probably involving the vegetative nervous system of which there has been much discussion. Some authors classify acrodynia as a vegetative neurosis.

PATHOLOGY

Although acrodynia has become a well-defined and fairly common clinical entity, reported examinations of the nervous system are not only meager but conflicting. This confusion is not only referable to the site of the lesion but to the pathology found. I will discuss briefly this variance of findings as found in the American papers.

General autopsy findings without those of the nervous system revealed very little in all cases reported. In those cases of long standing there was usually those findings of manifestations of a toxic disease such as fatty degeneration of the liver and kidneys but aside from this very little was noticed. However, in many cases it was surprising to find a generalized enlargement of the lumph nodes, expecially the mesenteric group. The microscopic study showing hyperplasia and degeneration of the lymphoid elements of the lymph nodes and spleen. Premature atrophy and degeneration of the thymus was found in several cases. Deamer and Biskind (20), Warthin (69) and Shostall made special reference to this. The rest of the systems in most cases were essentially negative with the exception of known secondary infections that were known to have occurred in several

instances, and were found at autopsy. It is rather unbelievable that such a debilitating disease could cause as little pathology as was found in these cases.

As the symptoms are quite referable to the nervous system, quite extensive studies have been made with quite a variance of findings, which I will endeavor to discuss. As the lesions are so non-discrete and variable. May I discuss this portion as to parts of this system, summarizing findings as recorded.

Brain:- Changes in the brain were found in approximately 33 1/3% of the cases. Warthin (69) showed that the meninges of the brain and cord showed edema and on section the brain showed edema and conjestion to such an extent that it was extremely wet. Microscopic studies varified this but there was no infiltration. These findings were varified by Shofstall. Blackfan's (4) case showed histologic evidence similar to encephalitis. Kernohan and Kennedy (43) reported chromotolysis in the basal ganglion, midbrain, medulla oblongata and gasserian ganglion, the cerebral cortex not being involved. They also discussed a central muclei with distinct rounding which was discussed by Wyllie and Stern (79) and shown that this region normally had this type of a cell so that the report was doubtful. Wyllie and Stern (79) in their report of seven cases, reported two cases which had cell-

ular infiltration in the cerebral cortex, above the medulla and in the basal ganglion. One of these had quite a large amount of round cell infiltration into the brain stem, cerebral cortex and basal ganglion. These were the most significant findings in the brain and many other reports were negative.

Spinal Cord:- About fifty per cent of the reported cases show distinct changes in the spinal cord and these were very inconsistent. More pathological changes were consistently found in the spinal cord than any other part of the nervous system. Byfield (11) reported gliosis of the central canal with poor staining of the anterior horn cells proximal to the commisure. Paterson and Greenfield (50) found a slight increase in glia in one case. In the other case they found a great increase of cells in the gray matter, especially in the lumbo-sacral region and ventral horns, where some of the large motor cells were swollen and contained eccentric nuclei and pole nissl granules. Wyllie and Stern (72) confirmed their findings in seven of their cases. Kernohan and Kennedy (43) reported only glial overgrowth. Orton Bender reported normal anterior horns and no glial overgrowth. Cobb (16) reported marked edema of the spinal cord with round cell infiltration and cellular degeneration. He did not state the cells involved. Orton and

Bender (49) reported a case in which the lateral columns of the spinal cord showed long standing degeneration, many of the cells remaining showing chromatolysis, fragmentation, and sclerosis. They stated that the lateral horns had a marked loss of myelin in comparison to the anterior horns and they stated a great similarity to the picture of poliomyelitis. The changes, in all cases reported, were more pronounced in the lumbosacral region. Paterson and Greenfield stated that the cells giving the picture of cellular infiltration was hard to determine the nature of. Lubin and Faber (42) report in their case that the intermediolateral cell column in the thoracic region contained many degenerating cells with extrusion of the nucleus, absence of nissl bodies, vacuole formation, and occasional shadow forms. They also report lumbo-sacral involvement of the anterior horn cells and posterolateral cell columns, there being marked chromatolysis, round and swollen cells, eccentric nuclei, and facuole formation. One can easily see the inconsistency of findings in these cases.

Involvement of the peripheral nerves occurred in several instances. Kernohan and Kennedy (43) reported that mainly all of the peripheral axons were invaded with demyelinization , and swollen axis cylinders. Paterson and Greenfield (50) also report the myelin

destruction in some fibers and stated that it increased as the nerves passed peripherally. He stated that the finer the nerves the more demyelinized it was. They also reported that only some nerve fibers were effected, others being apparently normal and this may account for the clearing up of the nervous symptoms after the disease process begins to clear. They stated that the cellular infiltration appeared to be from the sheath of Schwann. Wyllie and Stern (79) reported peripheral nerve involvement in four of the seven cases. The sympathetic nerves are usually unaffected. Deamer and Biskind (20) reported the lumbar sympathetic ganglions and chain had swollen and undergone chromotolysis and disappearance of cell outline indicative of neurophagia. Around some of the cells were phagocytic infiltration. Wyllie and Stern (79) report one case that died of a heart involvement in which the vagus nerve was the only nerve affected.

Simple atrophy was the only findings in the muscles. The nerve endings seemed apparently normal.

Pathological studies of the skin has been quite limited. Crawford (18) has probably written the best discussion on this phase of the disease and describes it quite well. He states that there is a marked hyperkeratosis and hyperplasia of the epidermis. There is slight acanthosis without parakeratosis. The inter-

papillary processes are lengthened and widened. There is no intercellular edema but the epidermal cells showed moderate intracellular edema. The papillary layer of the corium shows moderate mononuclear round cell infiltration, especially around the blood vessels and sweat glands. The sweat glands were increased and hypertrophical. Warthin (69) reports slight pigmentation of the rete. There was capillary dilatation but no edema of the papillary layer of the corium. Butler (10) reports ballooning of some of the cells of the granular layer. He states there is edema of the corium with infiltration of lymphocytes in clumps and some fibroblasts being present. Weber (70) verified these findings. The pathology of the skin has not been clearly gone into as the first case was reported in 1926 and little has been done since that time.

A review of the literature shows that reported cases of the pathology of acrodynia have been rather inconsistent. The findings have been referable to the nervous system, lymphatic tissue and skin. The findings of the nervous system have been the most inconsistent. Lubin and Faber (42) made an excellent review of the findings of the nervous system up until the present date, and showed their great inconsistencies. They concluded that the findings were inconsistent in occurrence, kind, and localization and hence do not offer a satisfactory explanation of the

clinical picture. They stated that since the clinical picture, nevertheless, quite consistently points to a disturbance of the sympathetic nervous system, it is desirable that further and more systematic search for lesions in this system be made.

TREATMENT

Until the etiology and pathology of acrodynia can be definitely decided upon, the treatment of acrodynia will remain a problem and symptomatic treatment still has to be resorted to. It is surprising the number of different types of treatment that have been instituted and the relatively good results that have been obtained from each type. I shall discuss the methods of treatment used and the results obtained.

The symptomatic treatment is of primary importance. The primary aim, in these unhappy children is to lessen discomfort and alleviate the mental and physical stress of the parents. The insomnia and irritability are marked and it is rather surprising that very large doses of the barbiturate derivatives have little or no effect. Harper (36) and Gonce (33) reported that the best sedation could be obtained from chloral hydrate. Harper (36) states that she used chloral hydrate and potassium bromide in conjunction with .015 to .03 grams of luminal three times daily and received fairly good results. Due to the extreme anorexia present, it often becomes necessary to give gavage feedings to prevent the extreme emaciation that sometimes takes place. Feedings should include a high caloric, high vitamin content.

This will be spoken of later. Harper (31) recommends small meals at frequent intervals. There should be no irritating fabrics near the skin. Silk or mercerized cotton is preferable and the bed clothes should be light. The youngsters should be allowed to assume any positions they care to. Atropine sulphate, five to ten drops of 1/1000 solution, is given four times a day to alleviate sweating and sialorrhea. The mothers should be instructed not to hold the patients as holding increases heat. Wood and Wood (78) state that all visitors should be kept away. Walks outside tend to allow sleep. They also suggest a tepid bath twice a day followed by drying and the use of methiolated spirits. Dusting liberally with talcum or zinc and starch powder frequently helps. They suggest keeping the mouth sterile by the use of hydrogen peroxide, one part to four parts of water on a swab for the patient to suck. Sweet (61) recommended a massage for the wasting muscles. Several authors have recommended the use of tincture of iodine on the skin to prevent secondary infections and ulcerations. Calamine lotion has frequently been applied to alleviate the skin irritation. One can easily see that symptomatic treatment is very essential though it gives poor results in comparison to most other disorders. The ideal thing is to have a nurse for the patient and treat the patient in the

home, as the mortality rises greatly from secondary infections when the children are hospitalized.

The most universally accepted specific treatment for acrodynia has been the use of a very high vitamin diet. In practically all of the reported cases this regime has been used and usually with quite favorable results. Several have reported no definite therapeutic improvement but in these cases the patient usually had an infection that they did not clear up. Wyllie and Stern (79) had a case without much improvement on vitamins in which they later started the use of raw liver therapy, keeping up the vitamins, and report full results due to the raw liver. Gladstone (32) reports a very advanced case in which he substituted two feedings of formula with five ounces of fruit juices and reported excellent results. Durand, Spicard and Burgess (22) report two cases in which they used 2000 units of Crysto-Vibrex for six days and all of the symptoms disappeared; stopping the use of this caused a recurrence of symptoms. They also treated the infectious element and reported that nicotinic acid given late did not hasten recovery. They also reported that treatment by mouth with a high vitamin B diet caused a relapse. McClendon (46) reports a case that began to clear in two weeks on a high vitamin diet and increased protein.

He also used irradiated ergosterol from which excellent results have been reported. Messer and Williams (44) likewise have reported excellent results with the use of irradiated ergosterol. This was also found to be true in the University Hospital. Wyllie and Stern (79) acting upon Findley and Stern's (26) rat acrodynia, that rats quickly improved with liver therapy, treated five cases with raw liver, cod liver oil and orange juice. They noted that the symptoms were apparently arrested in two weeks, the irritability and pain quickly subsiding. No cases relapsed. Braithwaite (7) reported that raw liver had a decidedly harmful effect. I believe that with the findings of today, we can honestly say that vitamin therapy has a distinct advantage and should be tried in every case.

Working on the infectious theory of the disease, Rodda (56) reported unusually favorable results with the removal of tonsils and adenoids. Schwartz (57) described motor paralysis of the left extremity that was greatly improved in five days after a tonsil and adenoid removal. Helmholz reported no improvement and Byfield (11) reported improvement after treatment of sinus infections. Muelchi (48) reported decided improvement in a case of long standing after removal of the tonsils and adenoids. Gareau (29) stated that a tonsillectomy and

adenoidectomy were very effective but in order to get good results it must be done early and in the incipient stage. It is the belief of some that the combination of treatment of removal of potential infections plus the high vitamin diet tends to give the best results.

Vipond (67) made an autogenous vaccine from an inguinal lymph gland and reported good results. He gave 1 c.c. of 5,000,000/c.c. as the first dose following in three days by 1½ c.c. He gradually increased the dosage to 5 c.c. He states that definite improvement was always found after the second dose and come to the conclusion that this treatment tended to cut off four to five months of suffering. It is the general accepted fact that treatment of the infections is a point that should not be overlooked. Sweet (60) reports good results with the use of ultra-violet light irradiations. He exposed the warm patients from two to ten minutes and gave this treatment twice each week. He used the radiant heat and the mercury vapor lamp. The results obtained caused Sweet to come to the conclusion that the patients can be cured within two weeks, which is a surprisingly short time. Braithwaite (7) reported this treatment to not have much effect. Frecker (28) gave a very good detailed method of ultra-violet light therapy and reported excellent results. He states that

the therapeutic effect due to exerting tonic effect upon the superficial ramifications of the sympathetic nervous system gives an effect which reflexly pervades the entire nervous system. He quotes Pacini as saying that through its distribution it reaches every cell in the body, and through its stimulation of the central nervous system, promotes a response that has been recognized clinically in the treatment of many conditions of radiant energy.

The treatment of acrodynia is very much discussed and has a variety of opinions as to the various effects of treatments. Not until the etiology and pathology of the malady is definitely established can the treatment be made specific.

DIFFERENTIAL DIAGNOSIS

The diagnosis of a case that has all of the cardinal symptoms is comparatively easy to recognize and should not be confused by anyone acquainted with the disease. The early diagnosis is based upon the mental and nervous symptoms with the findings of tachycardia and high blood pressure. In a clear cut case the cardinal symptoms on which a diagnosis is based are:

1. Recurrent rash appearing on the body and strongly and strongly resembles miliaria but changes appearance from time to time, accompanied by intense itching.
2. Hands and feet are swollen, red, and cold to touch. They appear like raw beef and perspire profusely.
3. Obstinate anorexia.
4. Softening of gums and falling out of teeth.
5. Leukocytosis.
6. Muscle weakness and atrophy.
7. Tendency towards chronicity.
8. Tachycardia and high blood pressure.
9. No fever, sore throat, or vomiting.

Bilderback (2) referred the diagnosis to the five "P's", namely:

1. Pinkness

2. Photophobia

3. Peeling

4. Paresthesias

5. Perspiration

To these Youmans (80) added prostration, pain, and popping--referring to the teeth involuntary "popping" out.

Byfield (11) gave an excellent differential diagnosis from pellagra in which he pointed out eleven various points, namely:

1. Lack of sharp line of demarcation of skin lesion.

2. Lack of definite common dietary error.

3. Uniform age of patient.

4. Absence of history of pellagra in the family.

5. Absence of digestive diseases.

6. Lack of recurrence of cured disease.

7. Low incidence of pellagra of similar disease.

8. Occurrences in breast fed infants.

9. Frequent history of infection.

10. Duration of subjective symptoms.

11. Aggravation of symptoms in cold weather.

Arsenic poisoning can be ruled out by the urine or blood chemistry. Wretchedness and emaciation and history rule out scarletina. Scurvy tends to occur later and

there is no blood in the urine or hemorrhage in the skin. Rickets usually occurs past the age of acrodynia and doesn't show the dermatitis. Foerster (27) points out that one can differentiate this from the common vitamin deficiencies by the fact of its lack of response to high vitamin diets. The cutaneous diseases usually have an abrupt onset with febrile reactions such as angina, high fever, and vomiting.

Of the dermatological conditions, most of them can easily be differentiated by the lack of the constitutional and mental symptoms seen in acrodynia.

PROGNOSIS

Prognosis of the disease process in itself is exceptionally good. It tends to have a high morbidity but a low mortality. Most of the reported deaths have been due to intercurrent infections, the main one being broncho-pneumonia. Wood and Wood (78) report a five per cent mortality in the home and a twenty-five per cent mortality in the hospital. The Alexandria Hospital of Sydney reports a twenty-four and one-half per cent mortality, which is exceptionally high. May I say that in practically one hundred per cent of the deaths there was a secondary infection present which was a big factor in causing the deaths. Broncho-pneumonia was present in two per cent of all acrodynia patients and fourteen per cent had pyuria. Otitis was frequently found and occasionally gastroenteritis and cerebral abscess were found.

The partial and complete paralysis has completely recovered in all reported cases and no residual findings following the disease have ever been recorded.

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